



(Billing Code: 4150-31)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Office of the Secretary

Findings of Research Misconduct

AGENCY: Office of the Secretary, HHS

ACTION: Notice.

SUMMARY: Notice is hereby given that the Office of Research Integrity (ORI) has taken final action in the following case:

Andrew Aprikyan, Ph.D., University of Washington: Based on the report of an investigation conducted by the University of Washington (UW), the UW School of Medicine Dean's Decision, the Decision of the Hearing Panel at UW, and additional analysis conducted by ORI, ORI found by a preponderance of the evidence that Dr. Andrew Aprikyan, former Research Assistant Professor, Division of Hematology, UW, engaged in research misconduct in research supported by National Cancer Institute (NCI), National Institutes of Health (NIH), grant CA89135 and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), NIH, grant DK18951, and applies to the following publications and grant applications:

- *Blood* pre-published online on January 16, 2003 ("NEM")
- *Experimental Hematology* 31:372-381, 2003 ("CMA")
- *Blood* 97:147-153, 2001 ("ISB")

- R01 CA89135-01A1
- R01 HL73063-01
- R01 HL79615-01

Blood pre-published online on January 16, 2003, has been retracted and *Experimental Hematology* 31:372-381, 2003, has been corrected.

Specifically, ORI finds that by a preponderance of the evidence, Respondent falsified and/or fabricated results relating to the above publications and grants. Specifically, Respondent:

1. falsely reported sequencing data in the NEM manuscript to strengthen the hypothesis that NE mutations contributed to the phenotype observed in severe congenital neutropenia (SCN) patients. Specifically:
 - a. Respondent falsely reported in Figures 2A and 3 that patient 3 had the R191Q neutrophil elastase (NE) mutation, when the majority of the sequencing experiments showed that the mutation was not present.
 - b. Respondent fabricated text (p. 12) reporting that sequencing of RT-PCR products confirmed the expression of the NE mutants in the SCN patients and that no mutations were present in the granulocyte colony stimulating factor receptor (G-CSFR) gene and the Wiskott-Aldrich Syndrome (WAS) gene in SCN patients, when based on the lack of original records the experiments were not performed. The false claim for G-CSFR sequencing was also reported in CA89135-03.

2. falsely reported a two-fold increase in apoptosis of human promyelocytic (HL-60) cells transfected with NE mutants compared to wild type NE in Figure 4A, NEM, Figure 6A, CMA, Figure 8, HL73063-01, and Figure 7, HL79615-01. Respondent used arbitrary flow cytometry data files to generate histograms with the desired result. The false results supported the hypothesis that the NE mutations were sufficient for impaired survival of human myeloid cells.
3. falsified NE and β -actin Western blots in Figure 4B *Blood*, pre-published online January 16, 2003, Figure 5B of the manuscript initially submitted to *Blood* April 2002, and Figure 6B *Experimental Hematology* 31:372-381, 2003, by falsely labeling lanes to support the hypothesis that accelerated apoptosis in mutant NE transfect HL-60 cells was due to the mutation and not the level of protein present. Specifically:
 - a. Respondent used portions of a single NE Western blot to represent: Figure 4B as HL-60 cells transfected with L92H, R191Q, and wtNE, when the cells were transfected with R191Q, P110L, and D145-152; Figure 5B as HL-60 transfected with wtNE, mutNE, and EGFP when they were cells transfected with NE mutants, P110L, D145-152, and 194
 - b. Respondent used portions of a single β -actin Western blot to represent: Figure 4B as HL-60 cells transfected with L92H, R191Q, and wtNE, when they were cells transfected with I31T, P110L, and G185R mutants; Figure 5B as HL-60 cells transfected with wtNE, mutNE, and EGFP, when they were cells transfected with P110L, I31T, and INE; Figure 6B as HL-60 cells transfected with G185R, mock,

D145-152, and P110L NE mutants, when they were cells transfected with I31T, P110L, G185R, and 32. The false β -actin Western blot in Figure 6B was also included in HL73063-01, Figure 8 (where the I31T lane was labeled correctly), and HL79615-01, Figure 7.

4. falsified the reported methodology for flow cytometry experiments in Figure 4A, NEM, Figure 1 and 2, and Tables 2 and 3, CMA, and Figures 4, 5, and 6, ISB, to validate the key hypothesis showing accelerated apoptosis in SCN and CN patients. The methodology claimed that flow cytometry experiments were gated for GFP+ populations, or that cell purity was greater than 96%, when based on the available original records, the experiments were not performed as stated.
5. falsified Figure 2, CMA, Figure 2, HL73063-01, Figure 3, HL79615-01, and Figure 5, CA89135-01A1, demonstrating that the overnight cultures of CD34+ and CD33+ bone marrow cells from SCN/AML patients showed normal cell survival, and only the CD15+ overnight cultures showed accelerated apoptosis, when the actual record available contradicted this result. Respondent used flow cytometry data files to generate histograms with the desired result to support the hypothesis that the progression from SCN to leukemia (AML) involves acquired G-CSFR mutations that override the pro-apoptotic effect of the NE mutations in primitive progenitor cells.

Dr. Aprikyan has entered into a Settlement Agreement in which he denied ORI's findings of research misconduct based on the UW Faculty Adjudication Hearing Panel decision. The settlement is not an admission of liability on the part of the Respondent. Respondent entered into the Agreement solely because contesting the findings would cause him undue financial hardship and stress, lead to lengthy and costly appellate proceedings, and he wished to seek finality. Respondent agreed not to appeal the ORI findings of research misconduct set forth above. He has agreed, beginning on March 12, 2013:

- (1) if within two (2) years from the effective date of the Agreement, Respondent receives or applies for U.S. Public Health Service (PHS) support, Respondent agreed to have his research supervised for a period of two (2) years; Respondent agreed that prior to the submission of an application for PHS support for a research project on which his participation is proposed and prior to his participation in any capacity on PHS-supported research, Respondent shall ensure that a plan for supervision of his duties is submitted to ORI for approval; the supervision plan must be designed to ensure the scientific integrity of his research contribution; Respondent agreed that he shall not participate in any PHS-supported research until such a supervision plan is submitted to and approved by ORI; Respondent agreed to maintain responsibility for compliance with the agreed upon supervision plan;

- (2) if within two (2) years from the effective date of the Agreement, Respondent receives PHS support, Respondent agreed that for two (2) years, any institution employing him shall submit, in conjunction with each application for PHS funds, or report, manuscript, or abstract involving PHS-supported research in which Respondent is involved, a certification to ORI that the data provided by Respondent are based on actual experiments or are otherwise legitimately derived and that the data, procedures, and methodology are accurately reported in the application, report, manuscript, or abstract; and
- (3) Respondent agreed not to serve in any advisory capacity to PHS including, but not limited to, service on any PHS advisory committee, board, and/or peer review committee, or as a consultant for a period of two (2) years beginning with the effective date of the Agreement.

FOR FURTHER INFORMATION CONTACT:

Director
Office of Research Integrity
1101 Wootton Parkway, Suite 750
Rockville, MD 20852
(240) 453-8200

David E. Wright,
Director
Office of Research Integrity